FORM PTO-1390 U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 3240-109
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	U.S. Application No. (if known) 10/559649

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/SG2004/000168	June 4, 2004	June 5, 2003

TITLE OF INVENTION
Cholesterol Biosynthesis Pathway Modulators and Uses Thereof

APPLICANT(S) FOR DO/EO/US
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Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [ ] This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.

4. [X] The US has been elected (Article 31).

5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not communicated by the International Bureau).
   b. [X] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)

6. [ ] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. [ ] is attached hereto.
   b. [ ] has been previously submitted under 35 U.S.C. 154(d)(4).

7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are attached hereto (required only if not communicated by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.

8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).

9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

ITEMS 11. TO 20. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A preliminary amendment.
14. [X] An Application Data Sheet under 37 CFR 1.76.
15. [ ] A substitute specification.
16. [ ] A power of attorney and/or change of address letter.
17. [ ] A computer-readable form of the sequence listing in accordance with PCT Rule 13*ter*.2 and 35 U.S.C. 1.821-1.825
18. [ ] A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. [ ] A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).

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20. [X] Other items or information:
Written Opinion of the International Preliminary Examining Authority,
Written Opinion of the International Searching Authority
Response to the Written Opinion
International Preliminary Report on Patentability
Published Application WO/ 2004/10928 A1 with International Search Report

21. The following fees are submitted:	CALCULATIONS	PTO USE ONLY
[X] Basic National Fee $300.00	$ 300.00	
22. [X] Examination Fee If the written opinion prepared by ISA/US or the IPER prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... $0 All other situations $200.00	$ 200.00	
23. [X] Search Fee If the written opinion of the ISA/US or the IPER prepared by IPEA/US indicates all claims satisfy provisions of PCT Article 33(1)-(4) ..... $0 Search fee (37 CFR 1.445(a)(2)) has been paid on the international application to the USPTO as an International Search Authority ..... $100.00 International Search Report prepared by an ISA other than the US and provided to the Office or previously communicated to the US by the IB ..... $400.00 All other situations $500.00	$ 400.00	
TOTAL OF 21, 22 AND 23 =	$ 900.00	
[ ] Additional fee for specification and drawings filed in paper over 100 (excluding sequence listing or computer program listing filed in an electronic medium). The fee is $250.00 for each additional 50 sheets of paper or fraction thereof.	$	

Total Sheets	Extra Sheets	Number of each additional 50 or fraction thereof	Rate		
- 100 =	/ 50 =		x 250	$	
Surcharge of $130.00 for furnishing any of the search fee, examination fee, or the oath or declaration later than 30 months from the earliest claimed priority date (37 CFR 1.492(h)).				$	

Claims	Number Filed	Number Extra	Rate		
Total Claims	38 -20 =	8	X $50.00	$ 400.00	
Independent Claims	6 - 3 =	3	X $200.00	$ 600.00	
Multiple dependent claim(s) (if applicable)			+ $360.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1,900.00	
[X] Applicant claims small entity status. The fees indicated above are reduced by 1/2.				$ 950.00	
SUBTOTAL =				$ 950.00	
Processing fee of $130.00 for furnishing the English translation later than 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$	
TOTAL NATIONAL FEE =				$ 950.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$	
TOTAL FEES ENCLOSED =				$ 950.00	
				Amount to be refunded	$
				Amount to be charged	$

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a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 02-2135 in the amount of $ 950.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2135. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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CONFIRMATION

Our Ref: FP2262/GM

Your Ref: PCT/SG2004/000168

16 June 2005

FAX COPY – CONFIRMATION BY MAIL

No. of Pages 2 **Your Fax No. 001 61 2 6285 3929** **Our Fax No. (65) 6227 3898**

Dear Sirs,

Re: PCT Patent Application No. PCT/SG2004/000168
entitled CHOLESTEROL BIOSYNTHESIS PATHWAY MODULATORS AND USES THEREOF
in the name National University of Singapore

We refer to the Written Opinion of the International Preliminary Examining Authority of 5 May 2005.

The applicant respectfully disagree with the Examiner's comments. In response to the Examiner's objections in the Written Opinion, the applicant wishes to make the following written submissions.

Inventive Step

The Examiner has opposed to claim 24 and some of its dependent claims with respect to inventive step, citing D1 (Indian Heart Journal, 1986, Vol. 38, No.5, pages 369-372) as prior art. In particular, claim 24 relates to an isolated peptide having the function of HMGCoA reductase inhibitor, phosphomevalonate inhibitor, which reduces the accumulation of cholesterol and/or the level of serum cholesterol and wherein the peptide has a molecular weight of 16803 Da, 16790 Da, 16791 Da or 17211 Da.

D1 describes how the authors had induced acute myocarditis using red scorpion (*Buthus tamulus*) venom in dogs, as a model to study the effects of scorpion stings. The crude venom at 4mg/kg was injected intravenously in dogs to create the acute myocarditis. Blood was collected 40 minutes after the venom administration and was processed for serum total cholesterol, free fatty acids and phospholipids.

Based on the ECG findings, the authors reported an initial phase of hypertension followed by a hypotensive phase and the authors claimed that these effects were due to the release of massive amounts of catecholamines due to the venom administration. They further reported that the catecholamines activate specific lipases in adipose tissue and muscle, which then breaks down triglycerides to free fatty acids and glycerol. The increase in serum level of phospholipids was due to the epinephrine release during the envenomation.

As such, the authors were creating a model to study scorpion envenomation in dog and in the process observed that the release of catecholamines and epinephrines by the venom was responsible for acute myocarditis and the altered serum lipid profiles. However, there was no indication or suggestion of any protein or compound, nor its function or activity, in the venom that could be responsible for the reduction in total cholesterol and related products.

Therefore, a person skilled looking at whole the content of D1 would have not found any indication nor suggestion to look for a particular peptide in scorpion venom, let alone a peptide having a molecular weight of 16803 Da, 16790 Da, 16791 Da or 17211 Da. On the contrary, the skilled person was suggested that catecholamines and epinephrines were responsible of the altered serum lipid profile. Therefore, it would not have been obvious to a person skilled in the art to isolate a peptide having the above-mentioned molecular weights from scorpion venom.

In view of the above, the applicant respectfully requests that the Examiner reconsiders his opinion and finds that claims 24, 26-28, 31-36, 39 and 40 indeed have an inventive step.

We look forward to receiving the International Preliminary Report on Patentability (IPRP) in due course.

Yours faithfully,

Lloyd Wise, Singapore
Gianfranco Matteucci

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